DETAILED ACTION

Claims 1, 3-4, and 14-24 are pending.

Receipt and consideration of Applicants' remarks/arguments filed on filed on 01/24/2012 is acknowledged. Claims 19-20 remain withdrawn as being drawn towards a nonelected invention or specie. Claims under consideration are claims 1, 3-4, 14-18 and new claims 21-24.

Applicants' arguments, filed 01/24/2012, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of claims 1, 3-4, 14-18 and 21-24 under 35 U.S.C. 112, first paragraph is maintained, because the specification, while being enabling for the "**treatment** of dopaminergic cell loss in a subject or decreasing the progression of Parkinson's

disease", does not reasonably provide enablement for the "**Preventive treatment of Parkinson's disease**". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, and predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method for **preventive** treatment of Parkinson's disease in a subject suffering from, comprising administration of **rotigotine**. The nature of the invention is extremely complex in that it encompasses the actual **prophylaxis** of a neurological disorder (i.e. dopaminergic cell loss) such that the subject treated with above compounds does not contract Parkinson's disease. In other words, the instant claims are drawn to a composition and method of preventing all preclinical stages of any and all stages of Parkinson's disease, which includes any undetectable stages of the disease.

Breath of the Claims*:* The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass prevention of a complex cell degenerative disorder in humans which has potentially many different causes (i.e. many

different mutations or combination of mutations). Each of which may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification and working examples: The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to actually prevent Parkinson's is minimal. All of the guidance provided by the specification is directed towards **treatment rather than prophylaxis** of dopaminergic cell loss (i.e. Parkinson's disease). The examples recited in the instant disclosure recites treatment of animals in which experimental Parkinsonism's were generated by treating them with MPTP neurotoxin. The data presented just demonstrates the neuroprotective nature of rotigotine. It is noted that in instant disclosure does not present any examples or data showing the effect of the instantly claimed compound in preventing Parkinson's disease where in patients without clinically confirmed Parkinson's disease are treated with the instantly claimed drug.

The state of the prior art and the predictability or lack thereof in the art: The state of the prior art is such that it involves screening both *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. which compounds treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face.

While the state of the art is relatively high with regard to **treatment** of neurodegenerative disorders (i.e. Parkinson's disease), the state of the art with regard

to **prevention** of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of Parkinson's disease. The state of the art, Kase et al. (US 2004/0198753A1) teach that there is **no known cure** for Parkinson's disease and the treatment is **aimed at controlling the symptoms**. Kase et al. teach that most early Parkinson's disease patients respond well to symptomatic treatment with dopamine replacement therapy, but **disability increases with progression of the disease**. (Page 1, [0010]).

The lack of significant guidance from the specification or prior art with regard to the actual **prevention** of Parkinson's disease in a human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of **prevention of Parkinson's disease**.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for prevention of Parkinson's disease. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard prevention of Parkinson's disease with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of

administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding prevention of Parkinson's disease with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of Parkinson's disease in a subject by administration of the claimed compound.

Thus, factors such as "sufficient working examples", "the level of skill in the art", and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant claimed methods. In view of the breadth of the claims, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compound or combination of compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate with the scope of the claims.

Genetech Inc. V. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue

experimentation to test which diseases can be treated or prevented by the compound encompasses in the instant claims, with no assurance of success. Thus, rejection of claims 12-13 under 35 U.S.C. §112, first paragraph, is deemed proper.

Response to remarks/ arguments filed on 01/24/2012

Applicants traverse the 112 enablement rejection above with the following arguments.

(a) Nature of invention: Present application clearly defines "prevention" and "preventive treatment" of Parkinson's disease as encompassing not only preventing but delaying appearance or significant development of motor symptoms of the disease. The method of Claims 1 and 22 include identifying subjects without "clinically confirmed" Parkinson's disease, which means the patient population includes those that have less than two of the cardinal symptoms. They also argue that the specification, teaches that "[c]urrent clinical observations as well as anatomical and genetic research now show that it is possible to both diagnose patients with Parkinson's disease at an early stage and to identify high-risk patients" including, identifying eight (8) different diagnostic markers and further teaches that "[t]he earlier a therapy can be initiated, the greater the chances of a long-lasting prevention of the onset of symptoms that lower the quality of life.

With regards to this argument, examiner would like to point to the applicants that the "prevention" used in the instant claims is drawn to the prevention treatment of Parkinson's disease which reading broadly suggests that this treatment method

prevents the said subject from acquiring the Parkinson's disease this embodiment is supported by the definition of prevention in the specification. The nature of Parkinson's disease is such that it is incurable; however, there are number of different treatments that are available to improve quality of life and physical and psychological morbidity. While the applicants state in their arguments that the patient population include those that have less than two of the cardinal symptoms, it is noted that less than two includes zero (0) symptoms, which therefore encompasses any member of the population, as such treating a subject who has not shown any signs of acquiring Parkinson's symptoms is not enabled in the instant specification.

(b) Breadth of the claims: There is no suggestion in the claims that administration of rotigotine can address such causes of Parkinson's disease, including mutations or combinations of mutations. What Applicant first discovered is that rotigotine reduced neuron loss and it is known that "patients with Parkinson's disease only develop the motor disturbances once approximately 70% to 80% of the dopaminergic neurons in the substantia nigra (SN) have been irreversibly damaged."

Examiner finds this argument unpersuasive, the claim as instantly filed, is drawn to preventive treatment of Parkinson's disease, i.e. that by following the method process as recited in the claims, applicants will not develop Parkinson's disease. The main mechanism by which rotigotine acts according to the applicants is through decrease in the neuron loss in patients prone to Parkinson's disease. However, the instant claims does not recite this mechanism and, it is noted that the features upon which applicant relies (i.e., mechanism of action of rotigotine) are not recited in the rejected claim(s).

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further there is no indication in the subject population as instantly claimed that they are prone to dopamine neuron loss and as such would require the treatment recited in the claims.

(**c) Guidance of the specification and working examples**: Applicants argue that the majority of their specification is directed to neuroprotection]. The test results suggest that apoptotic processes are prevented by rotigotine" or simply put, the embodiments set forth in the specification establish that apoptotic processes believed to destroy dopaminergic neurons which causes motor disturbances in Parkinson's disease is prevented by rotigotine. The results in the specification as filed show that rotigotine improved the survival of the neurons and the nerve endings in relation to the dose. Accordingly, because the working examples used are a well-established prophylactic model and the degree of neuron loss was indicative of prediagnostic stage of the disease, Applicant submits that the data are sufficient to demonstrate preventive action of rotigotine.

While the examiner maintains that the " data presented [in the specification] just demonstrates the neuroprotective nature of rotigotine". The data however fails to set forth any results which demonstrate the prevention of Parkinson's disease in a subject. Applicants have not shown any clinical data demonstrating the preventive effects of rotigotine in acquiring Parkinson's disease. There is no clinical correlation presented where in this decrease in neuron loss by rotigotine indeed prevents one from acquiring

Parkinson's disease. Applicants demonstrate the activity of their compound using the MPTP model for Parkinson's disease (specification pages 16-17); wherein applicants demonstrate that rotigotine improved the survival of the neurons and their nerve endings depending on the dosage. While considerable amount of the neurobiology of Parkinson's disease is known, prevention of acquiring this disease is still not known, all the treatments to date remain palliative. It is known that most of the animal models, including the MPTP model for PD, are not able to perfectly replicate all features as a counterpart of the human disorder. Indeed Parkinson's disease is a disorder which mainly affects the elderly and shows a progression over decades, which cannot be achieved in an animal model designed to develop therapeutic strategies. While the MPTP model provides important contributions towards a better understanding of the mechanisms involved in nigrostriatal degeneration in PD, it is not predictive of the prevention of PD in subjects, Absence of evidence to the contrary.

(d) The state of the prior art: Applicant contest the implication that since others have not shown Prevention of PD, Applicant's specification as filed fails to enable long-lasting prevention of Parkinson's disease, Applicants argue that examples in the specification teach that if rotigotine is administered, neuron loss can be stabilized. The result of such stability is that a clinical diagnosis of Parkinson's disease (or early loss of pre- and postsynaptic dopaminergic neurons) is never made. Thus, although prior art may be limited on prevention of Parkinson's disease, one of ordinary skill in the art reading Applicant's invention disclosure, would not find it "highly unlikely" that

administration of rotigotine to patients without clinically confirmed Parkinson's disease would result in long lasting prevention of Parkinson' s disease.

This argument by the applicant is unpersuasive, applicants do not contest that the prior art is unpredictable with regards to prevention of PD (Parkinson's disease). Accordingly, Preventive treatment of Parkinson's disease with pharmaceutical agents can be considered as being nascent technology. It is noted in MPEP 2164.03 that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art are unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. ." The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If

one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one experiment or as in this case the use of MPTP model for PD. As such in the instant case, the unpredictability of the rotigotine having the same effectiveness in terms of inhibiting

neuron loss and consequently preventing PD upon treating human subjects is relatively high.

(e) Amount of experimentation necessary: Claims 1 and 22 are directed to a method and one of ordinary skill in the art does not need to engage in undue experimentation to prevent Parkinson's disease by administering rotigotine to a subject without clinically confirmed Parkinson's disease. The specification lays out the claimed method, for example, how to identify the subjects, how to administer rotigotine, the suitable dosages of rotigotine, and other active substances that rotigotine can be combined with. See, the specification as filed, at paragraphs [0059]-[006S]. No undue amount of experimentation is necessary to practice the invention as presently claimed, based on the disclosure in the present specification.

This argument by the applicant is unpersuasive. The specification, teaches treatment of mice which had PD induced by MPTP (specific concentration) with specific concentrations of rotigotine (0.3, 1 or 3 mg/kg) in a slow release formulation [0077]. Applicants further recite that there is dose related response, with 0.3 mg/kg showing very little effect whereas 3 mg/kg shows greater effect on neuron loss. It is not clear how this can be extrapolated in the preventive treatment of human subjects, who may or may not be prone to Parkinson's disease, since it is administered to subjects who may not have any clinical indication; it is not clear as to when the treatment has to be started and how the dosing is to be monitored (the recitation of the dosage in paragraph [0064] in the specification does not provide this teaching). In terms of experimentation, one of ordinary skill in the art will have to first develop a clinical trial to evaluate the preventive

capabilities of rotigotine for development of PD in humans, which would requires, determining the subjects to be in the study, which includes those with no symptoms of rotigotine, the dosage and duration of treatment, toxicity/side effect monitoring etc. and further monitor the patients for several years to evaluate if they are completely free from ever developing Parkinson's disease. Therefore there is undue experimentation to practice the instant invention as presently claimed.

Accordingly, applicant's arguments to the enablement rejection are found to be unpersuasive and the rejection is maintained.

Conclusion

Claims 1, 3-4, 14-18 and new claims 21-24.are rejected. No claims are allowed

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action. Any inquiry concerning this communication or earlier communications from the examiner should be directed to

SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-0541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/

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